MEDICAL STAFF CONFERENCE

The Prader-Willi Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* We have an interesting "paraendocrinologic" problem for presentation this morning. The case summary will be given by Dr. Homer Boushey.

DR. BOUSHEY:† The patient (Figure 1) is a 21-year-old Mexican-American male who first came to the surgical clinic in 1965 for correction of a left inguinal hernia and undescended testes. He was the eighth child born to a 41-year-old mother who had attempted to induce abortion with an unknown medication at two months' gestation. The attempt produced vaginal bleeding but not expulsion of the fetus. Fetal movements were decreased throughout gestation. Delivery was normal at term. The patient's birth weight was 4 pounds, 8 ounces. His siblings weighed between 7 and 8 pounds at birth. The patient's mother recalls that he was blue for the first three days of life and could not suck, gaining little weight in the first month. At age one month, he was admitted to the San Francisco General Hospital and stayed there for 30 days. Weight gain remained slow.

The patient's development was slow. There was little spontaneous movement for the first six months of life. He sat at one year, walked and talked at two and a half years, and was not toilet trained until five years of age. From the age of nine months to 13 years he had a number of grand mal seizures, which were poorly controlled with anticonvulsant medications. Since age 13 he has had no seizures, despite the withdrawal of anticonvulsant therapy. Intellectual growth has been impaired despite special schooling. He remains unable to read or write, and the full-scale intelligence quotient has been measured at 59. The patient's social adjustment, however, is apparently very sound. Although he was always short in stature, his weight was apparently appropriate for his height after the first year of life. At age 11 he started to gain weight rapidly. There is no persistent hyperphagia.

Medical history includes an operation for correction of right internal strabismus at age 8 and

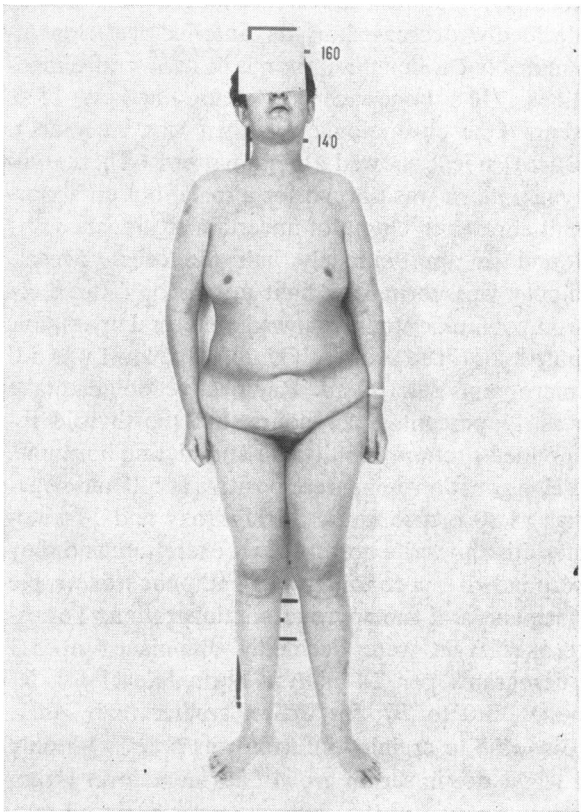

Figure 1. — Patient with Prader-Willi syndrome presented at this conference.

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multiple dental extractions at age 11 because of caries and malocclusion. At age 17 the height was 151 cm (—3 standard deviations for age) and the weight was 61.6 kg (falling within the mean for chronologic age and +3 standard deviations for height age). The patient's facies was characterized by close-set slit-like eyes, a beaked nose, low-set ears and a fish-like mouth with a high arched palate. There was some facial asymmetry, the right side being smaller than the left. Examination of the eyes showed slight ptosis of the right eyelid in addition to right esotropia and amblyopia exanopsia. The patient's habitus was generally feminine with subcutaneous fat distribution over the breasts and hips. The hands were small, described as elfin, with long, thin, delicate fingers. Examination of the genitalia revealed a small, uncircumcised penis with hypospadias; partially descended, small left testicle; and undescended right testicle. A left inguinal hernia was found. Neurologic examination revealed generalized hypotonia but was otherwise unremarkable. Because of these findings, the patient was referred to the metabolic service before corrective operation.

Evaluation on the metabolic ward included roentgenographic studies revealing a sella turcica decidedly decreased in its anterior-posterior diameter but wider than normal in its lateral dimensions. The bone age was determined as 15½ years (the chronologic age then was 18 years). Buccal smear showed a male pattern. The karyotype pattern was normal for a male, but an abnormal chromatin clump of uncertain significance was found in approximately half the cells. Muscle biopsy was normal by light microscopy, but electromyographic studies showed abnormal myopathic potentials. The protein-bound iodine level was 5.0 micrograms per 100 ml. Radioactive iodine uptake was 11 percent at 24 hours, but the thyroid responded promptly to thyroid-stimulating hormone. Urine gonadotropins were positive at 5.0 and negative at 80 mouse units. 17-Hydroxy and 17-ketosteroids showed a normal basal excretion, and they responded appropriately to adrenocorticotropic hormone and metapyrone administration. Testosterone levels were decidedly diminished at 3.3 micrograms per 24 hours (normal level for females, 5.0 to 20; for males, greater than 100). Response to arginine infusion was poor, with only a slight rise in serum growth hormone level (from a fasting level of 0.5 millimicrograms per ml to a peak level of 2.9 millimicrograms per ml at 30 minutes). An electroencephalogram showed diffuse slowing throughout. An electrocardiogram revealed early right ventricular hypertrophy which was confirmed by vectorcardiography. Prothrombin time, creatinine, phosphokinase, and alkaline phosphatase levels were within normal limits. The patient was referred to the urologic service for left orchipexy, inguinal hernia repair, and testicular biopsy. The biopsy specimen showed no evidence of spermatogenesis; the seminiferous tubules were lined only by Sertoli cells.

After discharge, the patient was seen once again in clinic for an effusion of the left knee. No cause could be found and the effusion resolved spontaneously.

Four days before the patient's second admission, a productive cough and fever developed, for which he was given tetracycline and a cough medication. He became lethargic and weak and was brought to the emergency room where an x-ray film of the chest showed left lower lobe pneumonia. The blood sugar level measured 1,450 mg per 100 ml with a serum osmolarity of 445 milliosmols per liter. The patient was not acidotic, and initially there was no acetonuria. A diagnosis of hyperosmotic, nonketotic, diabetic precoma was made, and treatment with intravenous fluid, insulin, and antibiotics was followed by prompt clinical improvement. With this improvement, it was possible to evaluate further the patient's pituitary function. Arginine and insulin infusions (Table 1) showed blunted growth hormone responses. A glucose tolerance test performed two weeks after recovery was decidedly abnormal and revealed a diminished insulin reserve (Chart 1). Following recovery the patient was discharged with no antidiabetic medications.

DR. SMITH: Thank you very much, Dr. Boushey. Perhaps we can see the films now, Dr. Sheft.

DR. SHEFT:* Our radiographic studies date back to 1966. At that time a film taken for skeletal age shows that the distal radial epiphyses, several of the metacarpal epiphyses, and the proximal phalangeal epiphyses are all open. This is quite abnormal in an 18-year-old male and reflects a bone age of approximately 15½ years. Notice the configuration of the fingers—very thin and very long. Although patients with the Prader-Willi syndrome sometimes have clinodactyly and syndactyly, this patient has neither of these findings.

*Douglas J. Sheft, M.D., Assistant Professor of Radiology.

TABLE 1.—*Results of Arginine and Insulin Tolerance Tests in Patient Presented*

Arginine Tolerance Test (30 grams given intravenously over 30 minute period)

	Test 1	*Test 2*	*Test 3*	*Test 4*
Time (minutes)	0	30	60	90
Blood glucose (mg per 100 ml)	164	178	174	148
Plasma growth hormone (millimicrograms per ml)	<1	7.1	5.3	4.0
Plasma insulin (microunits per ml)	<5	21	24	14.5

Insulin Tolerance Test (0.2 units per kg body weight given intravenously)

	Test 1	*Test 2*	*Test 3*	*Test 4*
Time (minutes)	0	30	60	90
Blood glucose (mg per 100 ml)	165	64	37	94
Plasma growth hormone (millimicrograms per ml)	1.0	. .	6.8	6.0

TABLE 2.—*The Prader-Willi Syndrome: Original Description*[1]

Extreme hypotonia in the newborn period without complete loss of the deep tendon reflexes.

Gradual improvement of the hypotonia during infancy and severe developmental delay.

Dwarfism with retarded bone age and generalized obesity by school age.

Cryptorchidism with flat hypoplastic scrotum and poor development of secondary sexual characteristics in boys.

Development of diabetes mellitus in older patients.

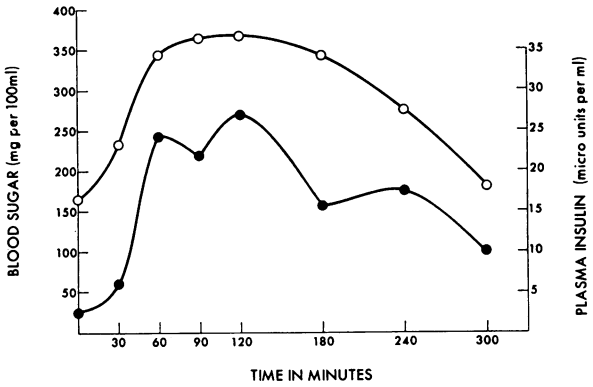

Chart 1.—Oral glucose tolerance test with simultaneous blood glucose and plasma insulin determinations in patient presented. 100 grams of glucose administered. o = blood sugar levels. • = plasma insulin levels.

Skull examination demonstrates an extremely small sella turcica and abnormal dentition. He has no teeth in his maxillary arch and several teeth remaining in his mandibular arch. The skull is rather short and brachycephalic, but the proportion between the face and the calvarium is normal. The posterior-anterior film of the skull reflects the narrowed orbits which Dr. Boushey described on physical examination. The bone density is normal.

A representative film of the patient's extremities suggests that there is pronounced muscle wasting. The bones are quite narrow; their maturation is delayed. Knee examination in 1966 showed a synovial effusion with distension of the suprapatella bursa. Also at that time the patient had some manifestations of arthritis in the hips.

DR. SMITH: We have asked Dr. Dennis M. Bier to open discussion concerning this unusual problem in paraendocrinology and metabolism. Dr. Bier is a graduate of the New Jersey College of Medicine and received his internship and residency training in pediatrics at the University of California Medical Center, San Francisco. He is currently a Research Fellow in the Cardiovascular Research Institute and in Pediatrics. Dr. Bier has been interested in this disorder and will begin by describing what is known about the syndrome.

DR. BIER: This patient probably represents an example of the syndrome which was first described in 1956 by Prader, Labhart, Willi, and Fanconi[1] at the Eighth International Congress of Pediatrics. Not all the features in this patient, however, are absolutely typical.

Prader and his colleagues described ten patients with similar clinical features (Table 2). Their original summation presents the major features of the syndrome. Approximately 125 patients were described or mentioned, and 13 years later their outline still represents essentially all that is known about the syndrome. In addition to the strong facial similarity between the patients, all had severe neonatal hypotonia, hypogonadism, dwarfism, mental retardation, and obesity. None of the features is diagnostic or unique in its own right, but the full complement of features appears to be distinctive enough to constitute a true clinical syndrome. It is likely that this syndrome is much more common than its description in the literature would indicate.

The sex distribution has been almost 3:1 males to females, but this may be only a reflection of the

TABLE 3.—*The Prader-Willi Syndrome: Prenatal Features*

Family history
Two patients with twins
A brother and sister with the syndrome
Parents of one case are cousins
DIMINISHED TO ABSENT INTRAUTERINE MOVEMENTS (42/50)*
Gestational bleeding
Length of gestation
TERM (51/77)
Longer than 40 weeks (19/77)
Less than 38 weeks (7/77)
Type of delivery
13 Breech
6 Caesarean section
BIRTH WEIGHT BELOW THE MEAN
20 Patients with intrauterine growth retardation

*The first number in parentheses indicates the number of patients exhibiting a particular feature. The second number indicates the number of patients in which the feature is mentioned in case history.

TABLE 4.—*The Prader-Willi Syndrome: Clinical Features During the Newborn Period*

Anoxia
MARKED HYPOTONIA
ABSENCE OF SPONTANEOUS ACTIVITY
WEAK TO ABSENT CRY
POOR SUCK AND SWALLOW
HYPOGONADISM
CRYPTORCHIDISM
FLAT HYPOPLASTIC SCROTUM
Thermoregulatory lability

TABLE 5.—*The Prader-Willi Syndrome: Clinical Features During Childhood*

History
DEVELOPMENTAL RETARDATION
Intelligence quotient 11 to 90
Seizures or loss of consciousness
Abnormal electroencephalogram (24/63)*
SLOW IMPROVEMENT IN HYPOTONIA
ACTIVITY
EATING
ONSET OF OBESITY (usually age 2 to 4 years)
HYPERPHAGIA
Rage reactions
Physical Characteristics
FACIES
FISH MOUTH
UPTURNED NOSE
ALMOND-SHAPED EYES WITH MONGOLOID SLANT
Herniae
Scoliosis
Strabismus
ACROMICRIA
Genu valgum
Microcephaly
HYPOGONADISM
SHORT STATURE
Small mandible
Dislocated hips
Acanthosis nigricans
Malocclusion and/or caries

*The first number in parenthesis indicates the number of patients exhibiting abnormal electroencephalogram. The second number indicates the number of patients in which abnormal electroencephalogram is mentioned in case history.

ease with which hypogonadism can be detected in boys. The clinical course can be divided into a number of phases which are listed in the next few tables. Features which have been so characteristic as to represent major manifestations of the syndrome appear in capital letters in the tables.

The family history (Table 3) is generally unremarkable. Two patients have had twin siblings. In the first case[2] the other twin was normal but "small." In the second case, one of our own series, the other twin died *in utero* approximately five days before delivery. Two other patients have come from the same family and another patient's parents were cousins.[3] However, the siblings had unusual clinical features, and the patient of the consanguinous parents did not have the prominent neonatal hypotonia which is one of the major manifestations of the syndrome.

The most characteristic feature of the gestational history (Table 3) is diminished intrauterine movements. This finding has led to the belief that the syndrome is, therefore, not related to those events that surround labor and delivery but is determined by some genetic factor or intrauterine insult. This hypothesis receives some support from the fact that the birth weights of children with the Prader-Willi syndrome are slightly below the mean birth weights of normal children of the same gestational age. Approximately 20 patients have had definite intrauterine growth retardation, with birth weights below the tenth percentile for gestational age. The length of gestation is usually normal, but 19 of the children have been carried longer than 40 weeks. Some of the mothers have had bleeding during pregnancy, and approximately 10 percent of the children were breech presentations.

At least 30 of these patients have had a definite history of birth anoxia (Table 4) which may complicate the diagnosis in early infancy. Most prominent in the newborn period is severe hypotonia with absence of spontaneous activity. In addition, because of their extremely poor suck and swallow, many have to be force-fed or fed by gavage for prolonged periods. One child was fed by gavage[2] and another by dropper[4] for the first five months of life. Also noticeable in the boys at birth is the small penis and flat, empty scrotum. An additional group

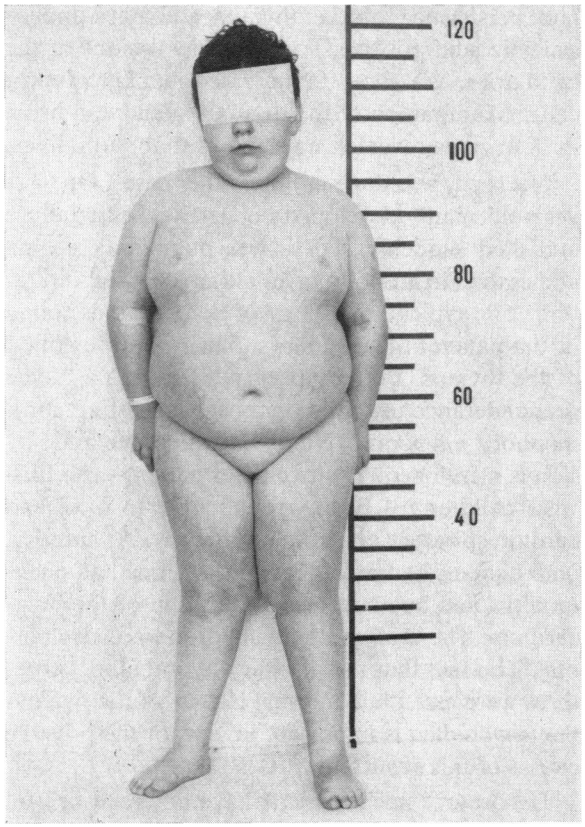

Figure 2.— Seven and one-half year-old boy with the Prader-Willi syndrome.

of infants have had some difficulty maintaining a stable body temperature.

In childhood (Table 5) there is gradual improvement in the hypotonia and feeding, but some hypotonia persists into adult life. In addition, these children have developmental retardation in all spheres. Most do not sit until they are one year old, do not walk until they are two, and do not talk until they are more than two years old. One patient never learned to walk[5] and another has not learned to talk.[6] The intelligence quotient estimates in later life have ranged from 11 to 90, but most of the children have quotients between 40 and 60.

Usually between the ages of one and four years obesity becomes apparent and is often accompanied by hyperphagia. Some parents have been forced to lock up food at home, and the children have been known to eat almost anything, including garbage. One child ate the cattle food on the farm where he lived.[7] Some patients also have periodic rage reactions, often related to having their desires for food thwarted.

A few children, including the patient today, have had seizures or episodes of unconsciousness during childhood, but these episodes have not persisted into adult life. Electroencephalographic studies have demonstrated multiple different dysrhythmias in 24 of 63 tracings.

TABLE 6.—*The Prader-Willi Syndrome: Clinical Features During Adolescence*

Boys	
DELAYED PUBERTY WITH POOR EXPRESSION INFERTILITY	
Girls	
GENITALIA USUALLY NORMAL	
Puberty and menses delayed in some	
Diabetes Mellitus	*Number of Patients*
Overt	10
Normal (test not specified)	10
Chemical diabetes (test not specified)	4
Normal oral glucose tolerance test only	24
Normal cortisone glucose tolerance test	15
Positive oral or cortisone glucose tolerance test	18
Total	81

Usually these children are short, although not severely dwarfed, and appear at the lower end of the normal scale. The facies is quite characteristic, featuring almond-shaped eyes having a Mongoloid slant, upturned nose, and a "fish-shaped," triangular upper lip. The hypogonadism found at birth remains, and two-thirds of the boys have bilateral cryptorchidism. The remaining boys usually have small testes located in the inguinal canals, and the scrotum remains flat and empty. Only two of the girls have had small external genitalia.[8,9] One of the most characteristic physical findings, felt by some investigators to be absolutely necessary for the diagnosis, is very small hands and feet with tapering fingers and toes. The patient presented today does not have true acromicria because he lacks the tapering, however, his hand abnormality has been described in some patients.

Strabismus, genu valgum, small mandible, and dental caries with malocclusion or enamel hypoplasia are among the more frequently associated features. Less common physical findings associated with this syndrome have included microcephaly, scoliosis, dislocated hips, inguinal herniae, and acanthosis nigricans.[8,10,11] This last feature is interesting because it is associated with a number of neuroendocrinopathies.

Many of these clinical features are demonstrated in Figure 2. This patient, a 7½-year-old boy, demonstrates the obesity, the slightly short stature and the characteristic facies. In addition he has right strabismus and genu valgum.

In adolescence (Table 6) the boys generally have diminished and delayed puberty with decreased secondary sex characteristics. Testicular biopsy in six postpubertal men, including the patient in present case, demonstrated atrophy or absence of spermatogenesis.[10,12,13] In one prepubertal boy,[14] no testis was found at herniorrhaphy. Three other prepubertal biopsy specimens were normal for the patient's age.[14,15,16] Another specimen showed very few spermatogonia and an absence of Leydig cells.[17] There has been no constant disorder in sexual maturation in the girls. One girl menstruated only once.[18]

Disorders of carbohydrate intolerance are usually discovered during adolescence or early adult life (Table 6). About 39 percent of those tested had a negative oral glucose tolerance test only, and 12 percent were described as having no diabetes, although the test procedures were not mentioned. No insulin measurements were made during these tolerance tests except in the patient presented today, who had a low insulin response to glucose. Dunn[19] determined plasma insulin levels after an oral glucose load of 1 gram per kg body weight in five of his patients. One of these patients, who had a diabetic response during a standard oral glucose tolerance test, had elevated insulin levels at one and two hours when compared with the normal control subjects. Fasting insulin levels in nine patients were within normal limits.[18,19,20] Despite the fact that diabetes occurs at a young age, it is characteristically non-ketotic and non-insulin dependent, resembling maturity-onset diabetes and responding well to oral hypoglycemic agents. The patient presented today has required neither insulin nor oral medications since his last hospital admission.

The prognosis in adult life is uncertain. The oldest living patient reported in the literature was 43 years old in 1966.[20] He had overt diabetes and an episode of diabetic gangrene of a toe. There is no further follow-up on this patient in the literature. Prader's oldest patient died at the age of 28 of renal failure, secondary to diabetic nephropathy, and resultant pulmonary edema. Recently Steiner[12] published the autopsy findings on this patient, as well as the postmortem results of another patient who died at 23 years of age and who had had chemical diabetes since age 19. The former patient had severe arteriosclerosis and glomerulosclerosis. There was an absence of glycogen in the liver and the myocardium. The latter patient died as a result of multiple pulmonary emboli. Both patients had persistence of the thymus and para-aminosalicylic acid-positive, homogeneous lesions of the capillaries, as well as an increased number of mast cells. Examination of the pituitary gland and brain in both cases revealed no significant abnormalities.

Necropsy was done in three other cases. One 42-year-old man[10] developed congestive heart failure and died suddenly. There was pulmonary edema and emboli in addition to an old myocardial infarction. The typical pathology of diabetes was found in the pancreas and kidneys. There is no mention of the thymus. In the pituitary, there was a "focal preponderance of chromophobes, suggesting chromophobe adenoma." No obvious hypothalamic lesion is mentioned. The two other patients who died were children.[9,21] Both were thought to have had cardiorespiratory syndrome of obesity. At autopsy, both patients had pulmonary edema, one had pneumonitis, and one had fatty infiltration of the myocardium. The brains in both children were also normal. The fact that the pituitary-hypothalmic structures were essentially normal in four of the five patients who died is important in view of the possible causes of this syndrome.

Laboratory investigations have not been helpful in establishing either the diagnosis or the cause of this syndrome. All routine hematologic studies, blood chemistries, and muscle enzymes have been normal. Lipid panels have been normal in the 40 patients tested. Skull x-rays are generally normal, but some patients show variations in skull shape (dolichocephaly, brachycephaly, turricephaly) or have a small sella turcica. The bone age is retarded in approximately 55 percent (39 of 71 patients). Pneumoencephalograms in 6 of 12 patients showed varying degrees of ventricular dilatation or cortical atrophy. Chromosome analyses were performed in 70 patients; 60 were normal. Two patients were possibly abnormal.[22,23] The remaining eight patients showed different patterns, including three patients with elongated Y chromosomes,[11,19] an XYY karyotype,[19] a balanced 14/18 translocation,[24] a 13/15 translocation,[17] a mosaic 13/15 trisomy,[22] and the patient today, who had an unusual chromatin body in 50 percent of the cells.

The electromyogram was normal in almost all instances with non-diagnostic findings in the others. Nerve conduction has been normal. Muscle biopsy has been normal in most patients. In one patient the findings were consistent with neurogenic atrophy,[25] and another patient showed finely beaded nerve fibers in the smaller bundles.[18]

TABLE 7.—*The Prader-Willi Syndrome: Differential Diagnosis*

	Syndrome			
	Prader-Willi	*Laurence-Moon-Biedl*	*Froelich*	*Lynch and Coworkers*[26]
Obesity	+	+	+	0
Hypogonadism	+	+	+	+
Mental Retardation	+	+	0	0
Dwarfism	+	0	+	+
Diabetes Mellitus	+	±	0	+
Diabetes Insipidus	0	+	+	0
Retinitis Pigmentosa	0	+	0	0
Family	0	+	0	+
Other	Hypotonia	Polydactyly	Central nervous system signs	Hyperlipemia

Urinary 17-ketosteroid and 17-hydroxycorticoid levels, including responses to the administration of adrenocorticotropic hormone and metapyrone, have been normal in general, although three patients did not show a satisfactory response to corticotropin or metapyrone.[6,8,17] Urinary gonadotropins have shown both high and low values. Growth hormone levels in five of Dunn's patients[19] and in the patient today were normal.

The major differential diagnosis of the Prader-Willi syndrome (after the infantile hypotonic period) is shown in Table 7. Although the Laurence-Moon - Biedl syndrome is associated with obesity, hypogonadism, mental retardation and, occasionally, diabetes mellitus, it is easily distinguished from Prader - Willi syndrome by its familial nature, the absence of dwarfism and infantile hypotonia, and the presence of retinitis pigmentosa, digital abnormalities, and diabetes insipidus. Froelich's syndrome, which is caused by lesions that produce hypothalamic destruction (usually craniopharyngiomas) is characterized by obesity, dwarfism, and hypogonadism. There is no mental retardation, infantile hypotonia or diabetes mellitus, however, and the obesity can start at any age. These patients, as originally described by Froelich, have signs of increased intracranial pressure with headache, vomiting and papilledema. In 1966, Lynch, Kaplan, Henn, and Krush[26] described a familial disease with hypogonadism, diabetes mellitus, and dwarfism. These children, however, were not obese and had no mental retardation. In addition, they had hyperlipemia and diabetes of the juvenile variety. A number of authors have suggested that the combination of severe infantile hypotonia and hypogonadism is so characteristic of the Prader-Willi syndrome that the diagnosis can be made before the onset of obesity and hyperphagia. Schneider and Zellweger[27] followed two infants with the characteristic facies and hypogonadism, who did not have obesity by four and six years of age respectively, and who were thus classified as *forme frustes* of the Prader-Willi syndrome. Today's patient resembles these children in that he apparently was of normal weight for his size until 11 years of age.

With regard to etiology, it is generally felt that gross chromosomal defect or birth injury can be excluded for reasons obvious from the previous discussions. Other possible explanations include some prenatal, physical, or chemical insult to the hypothalamic regulatory system; or a genetic, inherited metabolic defect. Both of these possibilities have counterparts in animals (Table 8).

The prototypes of hypothalamic injury are mice treated with gold thioglucose, which destroys the ventromedial nuclei of the hypothalamus, the so-called satiety centers. These mice are obese, hyper-

TABLE 8.—*The Prader-Willi Syndrome: Suggested Pathogenic Mechanisms*

Experimental Model	*Characteristics of Model*						
	Obese	*Hyperglycemic*	*Hyperlipemic*	*Fertile*	*Fasting Lipogenesis*	*Fed Lipogenesis*	*Mobilization*
Hypothalamic regulatory disturbance[28] (gold thioglucose mice)	+	0	+	±	0	+	+
Inherited metabolic disorder[28] (obese-hyperglycemic mice)	+	+	+	0	+	+	0
Prader-Willi *(in vitro)*[13]	—	0	0	—	+	—	0
Prader-Willi *(in vivo)*[33]	+	±	0	0	—	—	+

lipemic, and hyperphagic, but are not hyperglycemic. In addition, they have normal lipogenesis and can mobilize fatty acids from adipose tissue when hormone sensitive lipase is activated by catecholamines.[28] As was previously mentioned, however, patients with the Prader-Willi syndrome who have been studied at postmortem examination have had no obvious hypothalamic injury. An inherited metabolic defect might be similar to that of the obese-hyperglycemic mice. In the homozygous recessive state, these mice are, as their name implies, both obese and hyperglycemic in addition to being infertile and hyperlipemic.[28] These animals may have abnormal lipogenesis during fasting and poor mobilization of fatty acids from adipose tissue after stimulation of lipolysis with catecholamines.

The latter hypothesis has been advanced by Johnsen,[13] who presented *in vitro* studies with adipose tissue obtained from seven children with the Prader-Willi syndrome. The adipose tissue biopsy specimens "showed elevated palmitoleic acid levels suggestive of hyperlipogenesis." Also, "fat synthesis from acetate during fasting was tenfold greater than in tissue from unaffected sibs and hormone stimulated lipolysis was depressed." None of Johnsen's patients, however, were diabetic or hyperlipemic as are the obese-hyperglycemic mice. Further doubt has been cast on the specificity of Johnsen's hypothesis by Knittle's[29] recent demonstration that epinephrine-stimulated lipolysis in adipose tissue of obese children was decidedly decreased when compared with that of non-obese children. Thus, the poor hormone-stimulated lipolysis observed by Johnsen is not a specific pathogenic mechanism for the Prader-Willi obesity. In addition, preliminary results of our *in vivo* studies in six patients with this syndrome (four patients of our own and two of Doctors Sugarman and Boder) indicate that adults and children with the Prader-Willi syndrome have a normal rise in free fatty acids in plasma during a continuous norepinephrine infusion. Deficient lipolysis, therefore, does not seem to be present *in vivo*.

Finally, some observers have proposed a third etiologic possibility—that of an insulin antagonist similar to the one described by Vallance-Owen.[30,31] This synalbumin antagonist causes decreased incorporation of glucose into muscle but facilitates incorporation of glucose into adipose tissue. Significant insulin antagonism was demonstrated in one of six patients in Dunn's series.[19] That patient, a boy, was not diabetic and one of his brothers also showed the antagonist. Approximately 20 to 25 percent of the population is estimated to have this antagonist,[32] and its significance in the Prader-Willi syndrome is uncertain.

DR. SMITH: Thank you very much, Dr. Bier. We have time for comments or questions concerning this particular patient and this strange entity. Dr. Havel, do you have anything to add? Is this a lipid disorder?

DR.HAVEL:* I have really nothing to add to the excellent clinical description presented by Dr. Bier. I would like to congratulate Dr. Smith, who made the diagnosis in the patient presented today. This boy was studied in the Clinical Research Center two years ago and no diagnosis was established. Then the patient entered with hyperosmolar coma and was presented to Dr. Smith on ward rounds. He consulted the medical literature, and the diagnosis rapidly became apparent to him.

Dr. Bier and I have become interested in this syndrome and are studying a number of patients in the Pediatric Clinical Research Center. We are mainly interested in whether these patients have defective fat mobilization upon stimulation of hormone-sensitive lipase. We would also like to know about other aspects of the regulation of fat mobilization in these patients with respect to their tendency to accumulate adipose tissue.

In some respects, the reason I originally developed an interest in the Prader-Willi syndrome was related to my interest in total lipodystrophy. In many ways the clinical problems of these patients appear to be a mirror image of those presented in the Prader-Willi syndrome. Patients with lipodystrophy are not hypotonic; in fact, they are very muscular. Also, they have virtually no adipose tissue. Both conditions, however, have certain other features in common: The patients are mentally retarded, and they often present other suggestions of an endocrinopathy-acanthosis nigricans, for example. Patients with lipodystrophy have excessive fat mobilization in relation to their very small adipose tissue mass, and they may have a defect in the hypothalamus. We have wondered if some opposite defect might exist to account for some of the features of the Prader-Willi syndrome.

DR.SMITH: Thank you very much, Dr. Havel. I can assure you that this patient was presented to me

*Richard J. Havel, M.D., Associate Director of the Cardiovascular Research Institute and Professor of Medicine.

on ward rounds as a case of non-ketotic, hyperosmolar precoma in a diabetic, but I certainly did not know what the entire phenomenon represented. I only know that this entity was something quite different from anything I had ever seen, and I began a frantic thumbing of the literature. This patient is the first I have had occasion to see with this syndrome.

DR. CLINE:* What is the significance of Barr bodies in 50 percent of the cells with normal karyotypes?

DR. BIER: There were no Barr bodies, but some unidentified mass that stained with the characteristics of chromatin and was felt, possibly, to be an additional chromatin "dot." The karyotype will be repeated, I suspect, when the patient returns.

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